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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,011	07/16/2003	Julie D. Saba	200116.405C1	1654

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,011	SABA, JULIE D.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/14/08; 8/13/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14, 16, 20-22, 26-27, and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14, 16, 20-22, 26-27, and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-14, 16, 20-22, 26-27 and 30 are currently pending in the instant application.

Election/Restriction

In response to a previous Office action, a supplemental restriction requirement for patentably distinct polypeptides (mailed on 1/15/2008) and a final action (mailed on 3/12/2007), Applicants filed an amendment on 5/14/2008 amending claims 12, 16, 20 and 27, and cancelling claims 19, 23, and 31 is acknowledged.

Applicants' election of a polypeptide of SEQ ID NO: 21 or a nucleic acid encoding polypeptide of SEQ ID NO: 21 is also acknowledged. Claims 1-11, 15, 17-18, 24-25 and 28-29 remain cancelled.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2007 has been entered.

Claims 12-14, 16, 20-22, 26-27 and 30 are under consideration.

Applicants' arguments filed on 3/12/2007 have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

Previous rejection of claims 12-14, 16, 20-22, 26-27 and 30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement and scope of enablement is withdrawn in view of applicants amendment of claims 12, 16, 20 and 27 by limiting non-endogenous sphingosine kinase gene encoding protein of SEQ ID NO: 21.

Maintained- Claims Rejections- 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Previous rejection of Claims 12-14, 16, 20-22, 26-27, and 30 under 35 U.S.C. 103(a) as being unpatentable over Lanterman et al. (Biochem J. 1998 Jun 1; 332 (Pt 2): 525-31), Kim et al. (Genetics. 2000 Dec; 156(4): 1519-29) and in view of Melendez et al. (Gene. 2000 Jun 13; 251(1): 19-26 and GenBank Accession No. AF266756, created 6/1/2000) is maintained. The Examiner acknowledges that this application is not a joint invention, wherein the inventor is a single inventor.

Instant claims are drawn to a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway or any DPL1 gene or any LCB4 gene or any YSR2 gene and expressing a gene encoding a non-endogenous sphingolipid pathway component of a sphingosine kinase of SEQ ID NO: 21.

Applicants' argue that the cited references, taken individually or as a whole, do not teach or suggest an intact yeast phenotype rescue assay for screening inhibition of a non-endogenous SK. In fact, Lanterman *et al.* teach away from the present invention by disclosing that *(D,L)-threo-dihydrosphingosine,* a known inhibitor of mammalian SK, did not inhibit the yeast SK enzyme (see abstract, page 527, last paragraph and Figure 3), suggesting that molecular pathway components of the yeast sphingolipid metabolism system have significant structural and functional differences from the mammalian sphingolipid metabolism system and thus that the skilled artisan would lack an expectation that the mammalian SK would function in the yeast cell.

This is not found persuasive because yeast cells are widely used as a model to express human gene for functional studies of expressed protein or enzyme and method of use of said enzyme thereof, wherein expressed protein's function or activity depends on the enzyme structure, in particular binding domain and catalytic domain for the substrate, but not on the cellular factor, wherein a modulator may compete with substrate or binds active site thereby modulating enzyme activity. Cellular factor is not relevant because cellular factor only affects promoter activity of the expressed enzyme not the enzyme activity. Besides, human and yeast cells are eukaryotic cell, where cellular components and metabolic pathways are very similar in

both human and yeast cell than prokaryotic cell. Therefore, human SK will have similar function or activity in yeast cell like human cell. In addition, claims are not required to any inhibitor or use of yeast SK, but rather an assay of human SK activity by which a modulator can be identified in a well known yeast model system, which is taught by Lanterman et al., Kim et al. and Melendez et al. Therefore, applicant's conclusion is incorrect.

Applicants also argue that the skilled artisan would not have had a reasonable expectation that a non-endogenous SK protein would function in a yeast system. As such, the skilled artisan would have had no motivation to combine the teachings of Lanterman *et al.* with the teachings of either Kim *et al.* or with Melendez *et al.,* nor could such an artisan reasonably have expected to do so successfully. Even assuming, that there would have been motivation to combine the teachings of Lanterman *et al.* with the teachings of Kim *et al.* and Melendez *et al.,* Applicant submits that the teachings of these secondary references do not overcome the deficiencies of Lanterman *et al.,* namely the lack of teaching therein, as admitted by the PTO at page 12 of the Action, of the presently disclosed mutant yeast strains expressing a non-endogenous SK protein as recited in the instant claims.

This is not found persuasive because one of skilled artisan would expect that a known inhibitor of human SK would inhibit human SK in an yeast cell, if yeast cell is transformed with human SK gene and using said recombinant yeast cell system, one can screen inhibitors or activators of human SK for using human therapeutic purpose, and developing said recombinant heterologous yeast cell system is well known in the art. Besides, both human and yeast cell is eukaryotic cell having all the characteristics of eukaryotic cell including metabolic components and pathway, which is completely different than prokaryotic cells. Therefore, it is expected that

SK of Menendez et al. would function similarly in yeast cell, since human and yeast cell is eukaryotic cell. One of ordinary skill in the art would have been motivated to use human sphingosine kinase 1 (SPHK1) gene instead of yeast sphingosine kinase gene in order to obtain an agent or modulator of the human sphingosine kinase to use that agent as a therapeutic measure against human diseases like cancer and muscular disorders. Besides, this rejection was on obvious type of rejection under 35 USC 103, wherein all three references clearly teach all the limitation as well as a yeast assay system to identify agent which modulates SK activity.

Applicants' further argue that Kim *et al.* merely describe the further characterization of the biological role of phosphorylated long chain bases (LCBs) in yeast, and Kim *et al.* fail to cure the deficiencies of Lanterman *et al.,* in particular by providing no actual teaching or suggestion with regard to the use of non-endogenous SK in a yeast screening assay.

This is not found persuasive because Kim et al. indeed teach creating mutant yeast strain having mutations or inactivation of endogenous LCB4 (homolog of human SK), DPL1 and YSR2 same as the instant application, but do not teach expression of human SK, which is taught by Melendez et al. Kim et al. do not need to teach every element of the claimed invention in a rejection under 103.

Furthermore, applicants argue that Melendez *et al.* merely confirm that the human SPHK1 protein is indeed inhibited by these two well known sphingosine kinase inhibitors, and this SPHK1 inhibition is shown by simply exposing mammalian cell extracts to the inhibitors. No teaching or suggestion, however, is made by Melendez *et al.* of an assay involving intact yeast mutant strains, as would be required to practice the recited step of culturing a mutant yeast strain, nor do Melendez *et al.,* alone or in combination with any other documents, even remotely

contemplate screening other compounds for their ability to inhibit SPHK1, nor is a step of culturing yeast having non-endogenous SK in any way suggested.

This is not found persuasive Melendez *et al.* indeed teach a method of inhibition of human SK in COS cells by using two different well known SK inhibitors, which is not simply exposing the cell but Melendez et al. made a transformed COS cell expressing human SK, incubated said cell with SK inhibitors, isolated the cell extract and measured the SK activity (Fig. 4), which is correlated with the dose of the inhibitors. Although, Melendez et al. do not teach using yeast cell or assay by looking the growth of the yeast cell, but Lanterman et al. and Kim et al. indeed teach phenotypic assay by looking yeast cell growth, and one of skilled artisan would be motivated to replicate the method of Melendez et al. in yeast cell system as taught by Lanterman et al. and Kim et al. Besides, Lanterman et al. clearly teach mutant yeast strain (delta DPL1) has growth inhibition in presence of 50 uM sphingosine (Fig. 7).

Applicant submits that the primary and secondary references, taken individually or for what they teach as a whole, do not teach or suggest the claimed invention and in fact teach away from the present invention. Additionally, Applicant respectfully points out that the United States Supreme Court has recently noted that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.,* 550 U.S. (April 30, 2007, No. 04-1350; see also 82 U.S.P.Q.2d 1385; 127 S. Ct. 1727; 167 L. Ed. 2d 705; 2007 WL 1237837), citing *United States v. Adams,* 383 U.S. 39. Therefore, Applicant submits that the claimed invention would not have been obvious to the ordinarily skilled artisan at the time of filing.

Applicant's amendments to the claims and arguments have been fully considered but are not deemed persuasive to overcome the rejection on obviousness issue under 35 USC 103.

As described previous office action, Lanterman et al. teach a method of identifying an agent using yeast strain by measuring the production of sphingosine-1-P, which reflects the activity of sphingosine kinase, whether the kinase is inhibited or not in presence or absence of the candidate agent. Lanterman et al. also teach the creation of mutant strain, which comprises a null allele of DPL1 (dihydrosphingosine phosphate lyase) gene and an active LCB4 (kinase of sphingolipid pathway). Lanterman et al. further teach that the Δ DPL mutant yeast is extremely sensitive to sphingosine owing to its inability to degrade S-1-P and in presence of extracellular D-erythro-sphingosine results in accumulation of S-1-P, which is toxic to the cells and inhibits cell growth. However, double mutants of Δ DPL and Δ LCB4 do not have growth inhibitory effect of extracellular D-erythro-sphingosine because kinase mutant yeast strain comprising Δ LCB4 does not produce S-1-P molecule. It would have been obvious to one of ordinary skill in the art to use this system to identify an agent, which would inhibit kinase, which produces S-1-P as Lanterman et al. clearly show that the Δ DPL1 are growth inhibited only in the presence of an active sphingosine kinase. Lanterman et al. do not teach mutant yeast strain comprising null allele of endogenous YSR2 phosphatase gene and transforming said mutant strain with non-endogenous human SPHK1 gene encoding human sphingosine kinase 1, which is complimentary to LCB4 of yeast sphingosine kinase, which is mutated in the mutant yeast strain and expressing said SPHK1 gene.

Kim et al. disclose a method of analyzing sphingolipid metabolism in a mutant S. cerevisiae having disruption mutants of DPL1 (lyase), or LCB4 (kinase), or YSR2 (phosphatase) or in combination and assay methods of sphingolipid metabolism. Kim et al. also disclose that when DPL1 and YSR2 genes are mutated in yeast strains, it results in the enhancement of sphingosine-1-phosphate (S-1-P) level either in the culture medium or inside the cell to growth inhibitory levels but that Δ DPL1-LCB4-YSR2 triple mutant does not accumulate toxic levels of S-1-P. Kim et al. further teach that over expression of LCB4 i.e. kinase in triple mutant yeast strain Δ DPL1-LCB4-YSR2 results in the 500 fold accumulation of S-1-P than control, which is also extremely growth inhibitory to the mutant cells comprising triple mutant Δ DPL1-LCB4-YSR2 yeast strain, but over-expression of LCB4 in wild type yeast strain do not have such effects. As such Kim et al. clearly show that the triple mutant strains growth inhibited only in the presence of an active heterologous sphingosine kinase gene. Kim et al. do not teach method of screening agents by using mutant yeast system and transforming said mutant strain with non-endogenous human SPHK1 gene encoding human sphingosine kinase 1 and expression.

Melendez et al. teach a human sphingosine kinase (SPHK1), molecular cloning, and expression in host cells, functional characterization and tissue distribution. Melendez et al. also teach that sphingosine-1-phosphate (SPP), the product of sphingosine kinase, is an important signaling molecule with intra- and extracellular functions. Melendez et al. further teach an assay method to identify an inhibitor such as D,L-threo-dihydrosphingosine or N,N-dimethyl-sphingosine, which inhibit the human SPHK1 kinase and subsequently alter the sphingolipid metabolism.

Contrary to applicants arguments Lanterman et al. and Kim et al. indeed teach assay method of sphingosine kinase (SK) by which an activator or inhibitor of SK can be evaluated in terms of S-1-P formation. Lanterman et al. and Kim et al. also teach yeast strain null of DPL1 or LCB4 or YSR2 or double or triple mutant strain, although do not teach using a human SK. However, Melendez et al. teach a human SK and an assay method to identify an inhibitor such as D,L-threo-dihydrosphingosine or N,N-dimethyl-sphingosine, which inhibit the human SPHK1 kinase and subsequently alter the sphingolipid metabolism.

Thus, It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Lanterman, Kim and Menendez et al. to assay for inhibitors of human sphingosine kinase 1 (SPHK1) gene to identify an agent by using mutant Δ DPL1 and Δ LCB4 or a Δ DPL1, YSR2, LCB4 yeast strain transformed with said human SPHK1 gene, which modulates sphingolipid metabolism by monitoring either 1) the growth of mutant Δ DPL1, Δ LCB4 or Δ DPL1, YSR2, LCB4 yeast strain, as Lanterman et al. and Kim et al. each show that these strains are growth inhibited in the presence of an active sphingosine kinase such as SPHK, or 2) the concentration of S-1-P, which would decrease if the agents were active. It would have been obvious to one of ordinary skill in the art to identify an agent which alters the growth of mutant yeast strain or accumulation S-1-P concentration to identify an agent would be expected to prevent human diseases like cancer and muscular disorders in which S-1-P enhances cell proliferation, calcium mobilization or Raf/MEK/ERK signaling pathway or decreases apoptosis.

One of ordinary skill in the art would have been motivated to use human sphingosine kinase 1 (SPHK1) gene instead of yeast sphingosine kinase gene in order to obtain an agent or modulator of the human sphingosine kinase to use that agent as a therapeutic measure against human diseases like cancer and muscular disorders.

One of ordinary skill in the art would have a reasonable expectation of success because use of non-endogenous human gene to isolate agents or modulators, in a mutant yeast strain having disruption of endogenous genes are customary and widely used in the art.

Thus, for the reasons above and as discussed previous office action, the rejection is maintained.

Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed, can be reached on34. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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